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PATENT DEPARTMENT
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EXAMINER

NEREMOVA, V. EPS

ART UNIT	PAPER NUMBER

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10

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 2/95)

Office Action Summary

Application No.	Applicant(s)
09/866,296	Woltering et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Feb 3, 2003*.

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-13 and 38-41* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-13 and 38-41* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. [X] Notice of References Cited (PTO-892)
2. [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). 13
4. [ ] Interview Summary (PTO-413) Paper No(s). _____
5. [ ] Notice of Informal Patent Application (PTO-152)
6. [ ] Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/03/2003 has been entered.

Status of claims

Claims 1-13 as amended and new claims 38-41 [Paper No. 12 filed 2/03/2003] are under examination in the instant office action.

Claims 14-37 were canceled by applicants [Paper No. 12 filed 2/03/2003] as drawn to nonelected inventions.

Response to Arguments

Applicants' amendments and arguments filed 2/03/2003 have been fully considered but they are not persuasive for the reasons below.

Claim Objections

Claims 1-13 as amended and new claims 38-41 are objected to because of the following informalities:

Claim 1 appears to contain some typing error such as the use of coma before "and" on line 8. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-13 as amended and new claims 38-41 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as explained in the prior office action and for the reasons below.

Claim 1 as amended is rendered indefinite by the phrases "other cells of the tissues" followed by "including blood vessels, supportive stromal elements, neural cells and endothelial cells" because it is unclear whether the limitations following the phrase "other" cells are part of the claimed invention. It appears from the as-filed specification that "blood vessels, supportive stromal elements, neural cells and endothelial cells" are examples of the "other" cells which might derive from a particular tissue sample rather than they are all required to be within the tissue sample in the method for assaying angiogenesis (see specification page 28, last par.).

Claim 1 remains indefinite with respect to the phrase "if any" as explained in the prior office action. The purpose of the claimed process of assaying angiogenesis in the absence of angiogenic vessels is unclear and the method is incomplete as claimed because the angiogenic vessels are considered to be the blood vessels with endothelial cells which are required to be present as encompassed in the step (a) of the claimed method. In the alternative, if "angiogenic vessels" are not the blood vessels or blood vessels with endothelial cells, it is uncertain what is regarded as "angiogenic vessels" in the lack of definitions and, thus, it is uncertain what kind of

vessels is monitored in the process of assaying angiogenesis. Therefore, the method as claimed is indefinite and incomplete.

Claim 1 remains indefinite with respect to the phrase "time sufficient" as explained in the prior office action. Applicants argue that the use of functional language is permitted in the claims (response pages 6-7). However, a functional limitation or language must be evaluated and considered in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step. MPEP 2173.05 (g). In the instant case, either definitions of "angiogenic vessels" or the presence of "angiogenic vessels" is uncertain in order to define a particular "time sufficient" for assaying angiogenesis.

Claim 2 remains indefinite with respect to the phrase "substantially" as explained in the prior office action. Applicants argue (response pages 7-8) that the term "substantially" is definite because one of ordinary skill would understand the meaning of limitation in question. MPEP 2173.05 (b), subheading D. Yet, neither specification nor claims provide particular definitions of amounts which are included or excluded by the phrase "substantially". Moreover, the nature and the amounts of "angiogenesis-enhancing factors" or "angiogenesis-suppressing factors" are the results of the claimed method for assaying angiogenesis and they are the post-process knowledge. Thus, the amounts of factors or amounts of test compounds would not be readily known in the beginning of the method for assaying angiogenesis.

Claim 40 is indefinite and has an improper Markush group since it is uncertain what is included and what is excluded from the invention as claimed. For example: the use of "pancreatic

tissue" is repeated twice but the differences between tissues are uncertain as intended. It is unclear what is "a tissue from a wound" or what are components/structure of "a tissue from a wound", particularly in view that the claimed tissue is required to be intact (see claim 1, line 9). It is unclear what is encompassed by "a transplanted tissue" in the claimed method for assaying angiogenesis *ex vivo* or *in vitro* (claim 1, line 1).

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,856,184 [A] has been withdrawn.

The claimed method as amended excludes the use of an isolated artery or an isolated vein meaning that the isolated artery or vein has been separated from the surrounding tissues in the method for assaying angiogenesis *ex vivo* (claim 1, last line). The cited patent teaches the method for assaying angiogenesis *ex vivo* wherein the angiogenesis is monitored by using isolated aortic segments which were dissected from fat tissues and further embedded into the matrix. Thus, the tissues sample of the cited patent appears to consist of an isolated artery without additional "other cells" which are required in the claimed method as presently amended.

Claims 1-6 and 13 as amended and new claims 39 and 40 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. [U] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample which comprises blood vessels and other cells of the tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium with or without serum, to the use of medium supplemented with various factors including vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) for observing differences in angiogenesis in various systems. Some claims are further drawn to the use of matrix such as fibrin. Some claims are further drawn to monitoring control tissues sample without addition of factors affecting angiogenesis. Some claims are further drawn to the use of tissues from wound or transplanted tissues in the method for assaying angiogenesis *ex vivo*.

The cited reference by Brown et al. [U] is relied upon as explained in the prior office action and repeated herein.

Brown et al. [U] teaches a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue sample such as human placental blood

vessel fragments a fibrin matrix, step of supplying the embedded tissues sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels as the result of addition of various factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) in the presence or absence of serum (see abstract and page 551, col. 1, lines 4-20).

With respect to new claim 39 the cited reference discloses monitoring of control tissues sample without addition of factors affecting angiogenesis, for example: fig. 7. With respect to new claim 40 the cited reference teaches the use of placenta as a source of a tissue samples which was extracted and/or sectioned and, thus, the tissue sample of the cited reference is either "a tissue from a wound" or "a transplanted tissue" within the meaning of the claimed invention.

Therefore, the cited reference anticipates all active steps and all structural elements of the presently claimed method.

With regard to the cited reference by Brown et al. applicants argue that the tissue sample with isolated blood vessels in the cited method for assaying angiogenesis *ex vivo* is outside of the definitions found in claim 1 as presently amended (response pages 13-14).

However, the claimed method as amended requires the exclusion of "an isolated artery or an isolated vein" but not the blood vessels *per se*. The reference discloses that blood vessels which were used in the method for assaying angiogenesis *ex vivo* were derived from human

placenta. The cited reference clearly distinguishes the tissue sample with the placental blood vessel fragments from the tissue sample with blood vessels of venular and arterial origins by reciting that "similar angiogenic response were obtained from blood vessels of venular and arterial origins" (page 550, col.1, two last lines) which means that separate sets of protocols were applied to samples with blood vessels of different origins. Thus, the tissue sample with the placental blood vessel fragments in the method for assaying angiogenesis *ex* of the cited reference does not consist of "an isolated artery or and isolated vein" within the meaning of the claimed invention. Although the cited reference recites that the tissues sample with placental blood vessels has been dissected and/or sectioned, it does not excludes the presence of "other cells" derived from placenta. The presently claimed method is unclear with regard to the nature of "other cells" of the tissue sample with blood vessels. Moreover, the cited reference teaches a successful angiogenesis in the tissue sample and, thus, either "angiogenic vessels" were the "other" cells or the endothelial cells were present in the tissue sample of the cited reference as required by the presently claimed method. It is reasonably believed that the endothelial cells were the within the tissue sample of the cited reference by Brown et al. [U] because angiogenesis starts by sprouting of endothelial cells according to the Textbook of Medical Physiology by Guyton (page 190, col. 2). Therefore, the tissue sample which is used in the method for assaying angiogenesis *ex vivo* of the cited reference by Brown et al. [U] is considered to be the same as required by the presently claimed method. Thus, the claimed invention is anticipated by the cited reference by Brown et al. [U].

Claims 1, 3, 4, 6, 7, 9 and 12 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Montesano et al. [V] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports the growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium supplemented with serum and/or with factors which affects angiogenesis. Some claims are further drawn to the use of matrix such as fibrin or collagen or agar in the method for assaying angiogenesis *ex vivo*.

The cited reference by Montesano et al. [V] is relied upon as explained in the prior office action and repeated herein.

Montesano et al. [V] discloses a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tissue samples of muscular and adipose tissues in a matrix of fibrin gel or collagen gel, step of supplying the embedded tissue samples with a medium that supports the growth of the tissue samples or MEM medium with serum, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of

observing or measuring the angiogenic vessels (see abstract, page 807 at section "Materials and Methods" and figures 1-2). The cited reference also teaches the use of agar as a matrix (page 872, par. 2, last line). The cited reference appears to disclose that all experimental systems were treated in identical manner using the same culture medium. The cited method is considered to use tissue samples identical to the samples of the claimed method because the cited samples are vascularized muscular and adipose tissue samples comprising blood vessels together with all possible "other cells" of the surrounding intact tissues which do not consist of "isolated" artery or vein.

With regard to the cited reference by Montesano et al. applicants argue (response pages 14-15) that the tissue sample in the cited method for assaying angiogenesis *ex vivo* is not the same as required by the presently claimed invention because it has been minced into small fragments and, thus, the cellular architecture of the small fragments it is not substantially intact as required by the presently amended method. Yet, the claimed method is not limited by steps of making/preparing a tissue sample before step of embedding. Moreover, the claimed tissue sample comprises at least one and more "cut" surfaces, and, thus, it has been sectioned and/or minced as the sample of the cited reference. Therefore, the cellular architecture of the remaining tissue sample fragments is the same for both samples as claimed and as disclosed by the cited reference, particularly in view that there is no minimum sample size *per se* for the applicants' method as argued. Moreover, the muscular and adipose tissue explants of Montesano et al. are clearly taught as an effective model for assaying angiogenesis *in vitro* or *ex vivo* (abstract) and, thus, whatever

sizes of fragments were used, they were sufficiently large to retain original "intact" cellular architecture in order to function as an angiogenesis model within the scope of the present invention which excludes "an isolated vein" or "an isolated artery" but includes "other cells" of the surrounding tissue.

Claims 1, 3, 4 and 11 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Lugassy et al. [W] as explained in the prior office action and for the reasons below.

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels. Some claims are further drawn to the use of medium with serum or factors which affect angiogenesis. Some claims are further drawn to the use tumor fragment as a tissue sample in the method for assaying angiogenesis *ex vivo*.

The cited reference by Lugassy et al. [W] is relied upon as explained in the prior office action and repeated herein.

Lugassy et al. [W] discloses a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding three-dimensional tumor tissue sample in a matrix, step of

supplying the embedded tissue samples with a medium that supports growth of the tissue samples, step of incubating the embedded tissue samples in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue samples and step of observing or measuring the angiogenic vessels. The cited reference discloses the use of a three-dimensional tumor sample which is rebuilt from lymphoma cells and angioma fibroblasts in the *in vitro* or *ex vivo* experimental system (see English abstracts at page 37) for observing angiogenesis or formation of cells having vascular nature (page 38, line 17). The matrix is collagen (page 37, last two lines) and the culture medium comprises serum and/or serum factors which affect angiogenesis (page 39, par. 7, line 4) within the scope of the presently claimed invention. The portions of the cited reference which are in English appear to discloses that the experimental systems were treated in identical manner using the same culture medium. Thus, claims 13 and 38 which require a comparative control culture system without additional factors are not included in the instant rejection.

With regard to the cited reference by Lugassy et al. [W] applicants argue (response page 16) that the tumor tissue/fragment of the cited reference is a "rebuilt" tumor model obtained from isolated cells and that the cited tumor tissue/fragment is a cell agglomerate rather than a tissue sample/fragment as encompassed by the applicants' invention. Although the specification definitions might be considered as excluding tumor cell agglomerates without vascularization (specification page 29, lines 5-10) as a material for assaying angiogenesis, it is noted that the features which applicants relied upon in arguments are not recited in the rejected claims.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The history of a tumor tissue sample or a tumor fragment is not recited in the claims. It is uncertain as claimed, as argued and as disclosed by applicants whether there would be some differences in the cellular architecture between the rebuilt cancer model of the cited reference and the tumor sample as intended in the present invention. Moreover, the tumor model of Lugassy et al. comprises at least two types of tissue including "other cells" such as lymphoma cells and angioma fibroblasts wherein the fibroblasts are "supportive stromal elements" which are presently claimed. The tumor model of Lugassy et al. comprises cells of vascular origin or "blood vessels" or "angiogenic vessels" (page 38, line 17) within the scope of the presently claimed invention as drawn to the use of a tumor fragment (claims 1 and 11) in the method for assaying angiogenesis.

Claims 1-6 and 13 as amended and new claims 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,976,782 [IDS, paper # 13].

Claims as explained above for the claim rejection over Brown et al. [U].

US 5,976,782 [IDS, paper # 13] teaches the method for assaying angiogenesis *ex vivo* (see examples 1-3) wherein the method comprises step of embedding three-dimensional tissue sample such as human placental blood vessel fragments a fibrin matrix (col. 9, line 21), step of supplying the embedded tissues sample with a medium that supports the growth of the tissue sample, step

of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels as the result of addition of various factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) in the presence or absence of serum (see col. 9, lines 45-51 and col.10, lines 40-45). The cited reference discloses monitoring of control tissues sample without addition of factors affecting angiogenesis (col. 9, line 25). With respect to claim 40 the cited reference teaches the use placenta as the source of a tissue samples which was extracted and/or sectioned and, thus, it is either "a tissue from a wound" or "a transplanted tissue" within the meaning of the claimed invention. The tissue sample in the method of US 5,976,782 comprises blood vessels and other cells of the surrounding tissue including endothelial cells and supportive stromal elements or fibroblasts (col. 8, lines 40-45), and, thus, it is characterized by cellular architecture of the similar tissue *in vivo*. The method of the cited patent teaches the use a tissue sample which is not an "isolated" artery or vein because it recites that samples with arterial and venular vessels were cultured in the separate experimental systems but the results were the same (col. 8, lines 49-50).

Therefore, the cited patent is considered to anticipated the presently claimed invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-13 as amended and new claims 38-41 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Montesano et al. [V] taken with Brown et al. [U], Lugassy et al. [W], US 5,976,782 [IDS, paper # 13] and US 5,856,184 [A].

Claims are directed to a method for assaying angiogenesis *ex vivo* wherein the method comprises step of embedding a three-dimensional tissue sample in a matrix, step of supplying the embedded tissue sample with a medium that supports growth of the tissue sample, step of incubating the embedded tissue sample in the medium for a time sufficient to allow angiogenic vessels to growth into the matrix surrounding the tissue sample and step of observing or measuring the angiogenic vessels.

The claimed tissue sample comprises blood vessels and other cells of the surrounding tissues, it is characterized by cellular architecture of the similar tissue *in vivo*. The claimed tissue sample is not an "isolated" artery or vein meaning that it comprises other cells together with fragments of blood vessels including arterial or venular or capillary blood vessels.

Some claims are further drawn to the use of medium supplemented with serum and/or various factors which enhance or suppress angiogenesis. Some claims are further drawn to the use of matrix such as fibrin, collagen, agar, or Matrigel. Some claims are further drawn to monitoring control tissue sample without addition of factors affecting angiogenesis. Some claims are further drawn to the use of various tissue samples including tumor fragments, tissues from a wound, transplanted tissue, cardiac muscular tissue, skeletal muscular tissue, liver tissue, thyroid tissue, etc. in the method for assaying angiogenesis *ex vivo*.

The cited references Montesano et al. [V], Brown et al. [U], Lugassy et al. [W] and US 5,976,782 [IDS, paper # 13] teach methods for assaying angiogenesis *ex vivo* wherein the methods encompass the use of three-dimensional system comprising tissue samples embedded into matrix and supplied with additional factors which affect, enhance or suppress angiogenesis as encompassed by the presently claimed method. The additional factors in the methods of the cited references include that which are presently claimed. Some of the cited references {Brown et al. [U], US 5,976,782} teach monitoring of control tissue samples without addition of factors as compared to the tissue sample with added factors but some of the cited references are missing this particular disclosure {Montesano et al. [V], Lugassy et al. [W]}. However, it would be obvious to use control samples in experimental systems in order to distinguish between test factors which affect, enhance or suppress angiogenesis since it is a reasonably expected as well as a regular scientific practice.

The matrix materials in the methods of the cited references Montesano et al. [V], Brown et al. [U], Lugassy et al. [W] and US 5,976,782 [IDS, paper # 13] include fibrin, collagen and/or agar but the cited references appear to lack a particular disclosure about Matrigel or gelatin. However, the patent US 5,856,184 [A] teaches the use of Matrigel which is a complex material comprising collagen, fibrin and gelatin as a suitable matrix for growing new blood vessels and for studying angiogenesis. Although the particular disclosure of US 5,856,184 [A] is directed to the use of "isolated" aortic segments, the other cited references {Brown et al. [U], US 5,976,782} teach that comparable angiogenic responses are obtained for all types of blood vessels including

arterial, venular or capillary in the method for assaying angiogenesis. Thus, all presently claimed matrix materials are suitable for growing new blood vessels and assaying angiogenesis. The references are in the same field of endeavor and seek to solve the same problems as the instant application and claims such as assaying angiogenesis, and one of skill in the art is free to select components available in the prior art. In re Winslow, 151 USPQ 48 (CCPA, 1966).

The cited references Montesano et al. [V], Brown et al. [U], Lugassy et al. [W] and US 5,976,782 [IDS, paper # 13] teach various tissue samples as models for *ex vivo* measuring, observing and assaying angiogenesis as explained above for each cited reference. For example: the reference by Brown et al. [U] and US 5,976,782 [IDS, paper # 13] demonstrate the use of tissues with blood vessels and other cells including supportive stromal elements and endothelial cells in the method for assaying angiogenesis *ex vivo*. The reference by Montesano et al. [V] discloses the use of muscular tissues or skeletal muscle tissues in a particular example and it teaches and/or suggests the similar applications for a cardiac muscle tissue or heart tissue (see page 872, par. 2, line 12) or for a liver tissue or for thyroid tissue (see page 872, par. 2, lines 12-14) in the method for assaying angiogenesis *ex vivo*. The reference by Lugassy et al. [W] discloses the use of a rebuilt tumor fragment in the method for assaying angiogenesis *ex vivo*. Further, the cited patent US 5,976,782 [IDS, paper # 13] teaches and/or suggests the use of a tumor sample from a patient in the method for assaying angiogenesis *ex vivo* (col. 11, lines 26-37).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the method for assaying angiogenesis *ex vivo* as presently claimed with a reasonable expectation of success in observing angiogenesis in various tissue samples including that which are presently claimed because the prior art references demonstrate successful applications of similar three-dimensional *ex-vivo* systems for various tissues samples for assaying angiogenesis *ex vivo*. Thus, one of skill in the art would have been motivated to use various tissues for studying angiogenesis for the expected benefits in identifying therapeutically active substances which affect, enhance or suppress angiogenesis in various tissues. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

With regard to the claim rejection under 35 USC § 103 applicants' arguments are drawn to a general allegation that the claim 1 defines a patentable invention as related to the use of a specific tissue sample of claim 1 (response page 18, par. 1). This is not found persuasive because the method for assaying angiogenesis as claimed is applicable to various vascularized tissue samples as demonstrated by the cited references.

No claims are allowed.

Information Disclosure Statement

The information disclosure statement filed 2/03/2003 have been considered and the copy of PTO-1449 is attached herein. Two references by Guilec et al. [IDS, Paper No. 9 filed 8/26/2002] are manuscripts but not official publications. They have been placed in the application file, but the information referred to therein has not been considered on PTO-1449 form as lacking publication dates and/or reference to journal or meeting. Information related to 09/196,259 which is now US 6,465,613 has been considered as indicated on the PTO-1449 attached herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651 VERA AFREMOVA

March 28, 2003. PATENT EXAMINER

V Afremova